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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/621,833 | 07/16/2003 | Don Segal | 54800-8023.US00 | 9297 |

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| EXAMINER | |
|---|---|
| WAX, ROBERT A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1653 | |

DATE MAILED: 06/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/621,833 | SEGAL ET AL. | |
| | Examiner | Art Unit | |
| | Robert A. Wax | 1653 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *08 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *14-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *02172004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

1. Applicant's election without traverse of Group I, claims 1-13 in the reply filed on March 8, 2006 is acknowledged. Claims 14-50 are therefore withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions.

The requirement is still deemed proper and is therefore made FINAL.

### *Information Disclosure Statement*

2. The information disclosure statement filed February 17, 2004 has been considered. Please see the attached initialed PTO-1449.

### *Drawings*

3. The drawings received on July 16, 2003 are accepted by the examiner.

### *Specification*

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code at page 18, line 26. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. Applicants need only delete, "http://" to disable the hyperlink. See MPEP § 608.01.

***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-5, 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Hellstrom et al., Mather and Hubbell et al.

Hellstrom et al. teach an antibody, specifically, L53, which specifically recognizes human carcinoma cells. The antibody may be conjugated to agents having anti-tumor effects including enzymes, see column 1, lines 28-34. They do not teach urease as a chemotherapeutic agent, nor do they teach the hydrophilic polymer.

Mather teaches another cancer-cell-specific antibody, mPA7, which can be conjugated to a therapeutic agent or to liposomes or other vesicles containing chemotherapeutic compounds (see paragraph [0135]).

Hubbell et al., at column 16, lines 15, discuss entrapment of enzymes for chemotherapy. They first discuss enzymes including urease and then state, "Immunogenicity of these enzymes prevents direct use for chemotherapy. Entrapment of such enzymes in immunoprotective PEG gels, however, can support successful chemotherapy. A suitable formulation can be designed for either slow release or no release of the enzyme." They do not explicitly teach how to determine what molecular weight polyethylene glycol to use but at column 12, lines 9-16 they state that the molecular weight should be between 10,000 and 18,500 for encapsulating cells. In example 25, column 31, they use PEG with molecular weight of 10,000 for entrapment of catalase and state that this is sufficient to prevent diffusion of the catalase out of the gel. Clearly, then, if one wants to design a suitable formulation for slow release as suggested on line 15 of column 16, one is taught to select a PEG with a molecular weight lower than 10,000.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use urease as a chemotherapeutic agent in view of the teaching of Hubbell et al. that it is desirable to do so. Given that, one of ordinary skill in the art at the time the invention was made would have been motivated to combine the encapsulation of the urease with PEG and the targeting moiety such as the antibodies of Hellstrom et al. or Mather with the expectation of achieving an immunoprotected

chemotherapeutic agent targeted to the desired location by the selected antibody and, thus, an improved way to treat cancer. Claim 3 is included because the teachings of Hubbell et al. teach one of ordinary skill in the art to use PEG having a molecular weight less than 10,000 to create a controlled-release composition which includes the claimed molecular weight range.

8. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Hellstrom et al., Mather and Hubbell et al. as applied to claims 1-5, 11 and 12 above, and further in view of Houston et al.

The teachings of Hellstrom et al., Mather and Hubbell et al. are outlined above.

Houston et al. teach the use of the coiled-coil system for targeting a cytotoxic moiety to the proper cell.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the coiled-coil system taught by Houston et al. to target the urease to the correct place instead of the antibody system taught by Helstrom et al. and Mather et al. with the expectation of achieving at least the same level of selective targeting. The two targeting strategies are both known in the prior art and one of ordinary skill would expect successful targeting with either of the known systems.

9. Claims 7, 8 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hellstrom et al., Mather and Hubbell et al. as applied to claims 1-5, 11 and 12 above, and further in view of Deftos et al.

The teachings of Hellstrom et al., Mather and Hubbell et al. are outlined above.

Deftos et al. teach that liposomes are known as carriers for drugs, including targeted chemotherapeutic agents, see column 1, line 46 – column 2, line 13.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to place the targeting moiety-urease-PEG composite inside a liposome for delivery with the expectation of achieving the advantages taught for use of liposomes by Deftos et al. Since liposomes are similar to cell membranes and cell surface receptors are known.

10. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hellstrom et al., Mather, Hubbell et al. and Deftos et al. as applied to claims 7, 8 and 13 above, and further in view of Papahadjopoulos et al.

The teachings of Hellstrom et al., Mather, Hubbell et al. and Deftos et al. are outlined above.

Papahadjopoulos et al. teach that it is known to place targeting moieties onto liposomes for delivery of cytotoxic substances. See column 10, lines 5-9, where it states, "the liposomes bear ligands overexpressed by cancer cells and contain a cytotoxic agent. In this embodiment, the liposomes preferentially bind to any cancer cells in the cultured population, are internalized, and kill the cancer cells" and column 16, lines 57-62, where it states, "liposomes with targeting moieties such as antibodies or antibody fragments (such as Fab' fragments) or ligand for receptors overexpressed or preferentially expressed by a cell of interest (such as the folate receptor, which is overexpressed by some cancer cells) will preferentially bind to the targeted cells."

It would have been obvious to one of ordinary skill in the art at the time the invention was made to follow the teachings of Papahadjopoulos et al. and place the targeting moiety on the outside of the liposome with the expectation that successful targeting would occur.

11. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hellstrom et al., Mather and Hubbell et al. as applied to claims 1-5, 11 and 12 above, and further in view of Forney et al.

The teachings of Hellstrom et al., Mather and Hubbell et al. are outlined above.

Forney et al. teach that, " maintenance of homeostasis in tissues requires regulation of proteases (proteolytic enzymes) by endogenous protease inhibitors, which form complexes with and achieve selective inactivation of the proteases," see column 1, lines 61 –64.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a combination of urease and urease inhibitor in order to achieve the desired level of activity. Motivation for this comes from Forney et al., which serves as evidence that enzymes' level of activity, is known to be regulated by enzyme inhibitors.

***Conclusion***

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Wax whose telephone number is (571) 272-0623. The examiner can normally be reached on Monday through Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Robert A. Wax
Primary Examiner
Art Unit 1653

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